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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,427	05/31/2005	Marco Emilio Bianchi	1014-PCT-US	6913

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Albert Wai-Kit Chan
Law Offices of Albert Wai-Kit Chan
World Plaza Suite 604
141-07 20th Avenue
Whitestone, NY 11357

EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,427	BIANCHI ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 19-26* is/are pending in the application.

4a) Of the above claim(s) *19-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants response to the office action mailed on 4/21/2006, including arguments/remarks, and amendments to the claims, specification, and drawings, was received on 8/21/2006 and has been entered into the record.

2. In the amendment received on 8/21/2006, the Applicants cancelled claims 9-18 and have added new claims 19-26. Newly submitted claims 19-26 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: In the Applicants' response to the requirement for restriction, received on 1/20/2006, the Applicants elected Group I, claims 1-5 and 7-8, drawn to a *composition* of HMGB1 protein. The Examiner subsequently decided to examine claim 6 along with claims 1-5 and 7-8. New claims 19-26 are drawn to *methods* of tissue repair or regeneration. Original claims 1-8 are related to new claims 19-26 as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the composition of claims 1-8 can be used in a materially different process of using the product. For example, the composition of claims 1-8 could be used to raise antibodies specific for HMGB1 protein.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 19-26 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Therefore, claims 1-8 and 19-26 are currently pending. Claims 1-8 are the subject of this office action.

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found

allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

5. The text of those sections of Title 35, U.S.C. not included in this action can be found cited in full, in the previous office action mailed on 4/21/2006.

Information Disclosure Statement

1. The information disclosure statement received on 8/21/2006 has been fully considered by the Examiner.

2. Citations 1 and 11 in the information disclosure statement received on 12/22/2004 were not previously considered by the Examiner for reasons set forth on page 3 of the office action mailed on 4/21/2006. It is noted that complete citations 1 and 11 are presented in the information disclosure statement received on 8/21/2006.

Drawings

The objection to the drawings is maintained for the reasons set forth in PTO form 948, which was mailed with the previous office action on 4/21/2006.

Specification

Objection to the title as not being descriptive of the claimed invention is *withdrawn* in response to Applicants' amendment to the title to recite "Composition of HMGB1 protein".

Claim Objections

1. Objection to claim 1 for reciting non-elected subject matter, as set forth on page 3 of the office action mailed on 4/21/2006, is *withdrawn* in response to Applicants' amendment to the claim to delete the non-elected subject matter.

2. Objection to claims 6-8, as set forth on page 4 of the office action mailed on 4/21/2006, is *withdrawn* in response to Applicants' amendments to the claims to recite a "composition according to claim 1.....".

Claim Rejections - 35 USC § 112, second paragraph

Rejections withdrawn

1. Rejection of claims 1-8 under 35 USC § 112, second paragraph, as being indefinite for not defining the acronym HMGB1, as set forth on page 4 of the prior office action mailed on 4/21/2006, is *withdrawn* in response to Applicant's amendment to claim 1 to recite "a composition comprising an effective amount of the High Mobility Group One (HMGB1) protein".

2. Rejection of claims 1-8 under 35 USC § 112, second paragraph, as being indefinite in regards to "functional parts" of HMGB1, as set forth on page 4 of the prior office action mailed on 4/21/2006, is *withdrawn* in response to Applicant's amendment to the claims to delete the term "functional".

3. Rejection of claims 1-8 under 35 USC § 112, second paragraph, as being indefinite for due to the use of the phrase "and/or", as set forth on page 4 of the prior office action mailed on 4/21/2006, is *withdrawn* in response to Applicant's amendment to the claims to delete the phrase "and/or" from the claims.

4. Rejection of claims 1-8 under 35 USC § 112, second paragraph, as being indefinite regarding the term "regeneration", as set forth on page 4 of the prior office action mailed on 4/21/2006, is *withdrawn* in response to Applicant's amendment to the claims to recite "tissue regeneration".

5. Rejection of claims 2-8 under 35 USC § 112, second paragraph, as being indefinite regarding the term "depends from", as set forth on page 5 of the prior office action mailed on 4/21/2006, is *withdrawn* in response to Applicant's amendment to the claims to delete this term from the claims.

Claim Rejections - 35 USC § 112, first paragraph – enablement

Rejections maintained/necessitated by amendment

1. Claims 1-8 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of enablement for a composition comprising any HMGB1 protein or part, other than the full-length HMGB1 used in the examples of the specification, or tail-less HMGB1 (ABbt), as set forth on pages 5-6 of the prior office action mailed on 4/21/2006. The amended claims of the instant invention are drawn to a composition comprising HMGB1 proteins, or parts thereof, for the treatment of tissue damage or to promote tissue repair or tissue regeneration. The claims were previously rejected because the specification, while enabling for a composition for treatment of tissue damage or to promote tissue repair or tissue regeneration comprised of the full-length HMGB1 of the examples, or the ABbt fragment, is not enabling for any other HMGB1 protein or part thereof. In the response received on 8/21/2006, the Applicants argue that the specification shows at least one example of a part of HMGB1 that exerts the same activity on tissue regeneration as the full length HMGB1, namely the tail-less fragment ABbt, and therefore the

part of parts of the HMGB1 protein required to treat tissue damage or promote tissue repair or tissue regeneration is clear and definite to an ordinary skilled artisan.

These arguments have been fully considered and are not found persuasive. As set forth on page 6 of the office action mailed on 4/21/2006, the claims read on a composition comprised of all possible HMGB1 proteins, regardless of species. Although the specification provides examples using a full-length HMGB1 protein, the HMGB1 polypeptide of the examples is not identified by sequence, or by SEQ ID NO, and thus a skilled artisan would not be able to predict which of the many possible HMGB1 polypeptides was used in the presented experiments. The NCBI lists 37 HMGB1 polypeptide sequences; however, there is no guidance or examples in the specification showing that all possible HMGB1 polypeptides, from all possible species, would be functional in the claimed composition. Furthermore, the claims of the instant invention read on any "part" of any HMGB1 polypeptide. As set forth on page 5 of the office action mailed on 4/21/2006, the specification teaches that some parts of HMGB1 (i.e. the ABbt fragment) are capable of mediating chemotactic activity, but other parts, such as the didomain AB, are not. The claims, as currently amended, read on a composition comprising any "part" of HMGB1. Thus, although the skilled artisan would know the biological effects of ABbt and didomain AB, the skilled artisan would not know if any other "part" of HMGB1 would be capable of treating tissue damage or promoting tissue repair or tissue regeneration. Given the broadest reasonable interpretation, a "part" of a polypeptide such as HMGB1 could be as small as one amino acid, or even the hydrogen, carbon, oxygen, or nitrogen molecules that make up each individual amino acid. There is no guidance of examples in the specification of any single amino acid capable of mediating tissue repair or regeneration. The Applicants assert that "simple" experiments such as trypsinization of the full HMGB1 protein and subsequent functional characterization would allow one of skill in the art to determine which "parts" of HMGB1 would be useful in the claimed composition. Although the Examiner acknowledges that trypsinization experiments are routine and well-known in the art, the Examiner also notes that the criteria for enablement, as set forth in 35 U.S.C.,112, first paragraph, requires one of ordinary skill in the art to be able to "make and *use*", but not "make and *test*". Thus, a skilled artisan would require further, undue experimentation in order to make every possible "part" of HMGB1 protein, and then actually *use* these parts in a composition that promotes tissue repair or tissue regeneration.

In summary, the breadth of the claims, as currently amended, is excessive because the claims now read on a composition comprising any "part" of HMGB1 protein, wherein said part or parts is capable of use in a composition for treatment of tissue damage or to promote tissue repair or tissue regeneration. There is no guidance or examples in the specification that teach any "part" of HMGB1, other than full-length HMGB1 and the tail-less ABbt, that mediates tissue repair or regeneration, and therefore a skilled artisan would not be able to predict which of the many possible "parts" of HMGB1 would be useful in the claimed composition. The skilled artisan would therefore require further, undue experimentation to make and use any "part" of HMGB1, other than full-length HMGB1 or the ABbt fragment, in a manner that is commensurate in scope with the claims of the instant invention.

2. Claims 1-8 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of enablement for a composition comprised of HMGB1, or parts thereof, for treatment for damage, repair, or regeneration of any tissue other than cardiac tissue and mesangioblast stem cells, as set forth on pages 6-7 of the prior office action mailed on 4/21/2006. In the response received on 8/21/2006, the Applicants argue that the experiments performed pertaining to cardiac muscle or mesangioblast stem cells would be applicable to other tissues or cells, and therefore the specification is fully enabling for a composition comprised of HMGB1, or parts thereof, for treatment of damage to any tissue, or to promote repair or regeneration of any tissue. These arguments have been fully considered and are not found persuasive.

The breadth of the claims is excessive because the claims read on a composition for treatment of damage to any tissue, or repair or regeneration of any tissue. Although the instant specification provides guidance and examples showing that cardiac tissue and mesangioblast stem cells are responsive to HMGB1, there is no guidance or examples of a composition comprised of HMGB1, or any part of HMGB1, that is capable of mediating tissue repair or regeneration of any tissue other than cardiac tissue or mesangioblast stem cells. Furthermore, as set forth on page 7 of the prior office action mailed on 4/21/2006, the claims are further drawn to a composition for repair or regeneration of areas of necrosis. There is no guidance or examples in the specification that show how a composition comprised of HMGB1, or any part of HMGB1, can mediate the repair or regeneration of any tissue that is already dead, and a person of ordinary skill in the art would therefore not be able to predict how to make such a composition without further, undue experimentation.

In summary, due to the excessive breadth of the claims, which read a composition comprised of HMGB1, or parts of HMGB1, for treatment of damage to *any* tissue, or for the repair or regeneration of *any* tissue, the lack of guidance and examples in the specification showing that any tissue other than cardiac tissue and mesangioblast stem cells can be repaired or regenerated with the claimed composition, and the unpredictability inherent in the art regarding which tissues can be repaired or regenerated using a composition comprised of HMGB1, or any part of HMGB1, a person of ordinary skill in the art would require further, undue experimentation to determine which tissues, other than cardiac tissue or mesangioblast stem cells could be repaired or regenerated using the claimed composition.

Claim Rejections - 35 USC § 112, first paragraph – written description

Rejections maintained/necessitated by amendment

Claims 1-8 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of written description for a composition comprised of any "part" of HMGB1, as set forth on pages 7-8 of the prior office action mailed on 4/21/2006. The subject matter of the claims of the instant invention is discussed *supra*. In the response received on 8/21/2006, the Applicants argue that certain functional "parts" of HMGB1 have been exemplified in the specification, and that is it a matter of routine experimentation to generate other functional "parts". These arguments have been fully considered and are not found persuasive.

The instant specification describes a full-length HMGB1 protein that can promote proliferation and regeneration of cardiac tissue and mesangioblast stem cells, and also discloses a tail-less HMGB1, termed ABbt, that stimulates chemotaxis of mesangioblasts. However, the specification does not identify the full-length HMGB1 polypeptide of the examples by sequence or other descriptive means. Because there are many known HMGB1 polypeptides, from several species, the genus of full-length HMGB1 polypeptides capable of comprising the claimed composition has not been described. Furthermore, the amended claims are drawn to any "parts" of HMGB1. While the specification does disclose a tail-less HMGB1, ABbt, this example is not sufficient to adequately describe the claimed genus of HMGB1 "parts". As set forth above in rejection (1) under 35 U.S.C. 112, first paragraph – enablement, the term "parts" can be interpreted as any fragment, amino acid, molecule, or other "part" of an HMGB1

polypeptide. Other than the tail-less ABbt fragment, the instant specification does not adequately describe any other "part" of HMGB1 that is capable of mediating tissue repair or tissue regeneration. There is no particular structure or region of HMBG1 that must be conserved, other than full-length HMGB1 lacking an acid tail. There is also no description of any structure or sequence that a "part" of HMGB1 must possess in order to mediate the desired biological function of said part. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus of HMGB1 "parts".

Claim Rejections - 35 USC § 102

Rejections maintained/necessitated by amendment

Claims 1-5 and 7-8 *remain rejected* under 35 USC § 102(e) as being anticipated by Tracey *et al* (US 6,303,321), as set forth on pages 8-9 of the office action mailed on 4/21/2006. The claims of the instant invention are drawn to a composition comprised of HMGB1, or parts thereof. As set forth on page 8 of the prior office action mailed 4/21/2006, Tracey *et al* teaches a method of effecting weight loss or treating obesity, comprised of administering a composition comprising a HMGB1 protein. In the response received on 8/21/2006, the Applicants argue that Tracey *et al* does not teach treatment of tissue damage, tissue repair, or tissue regeneration, and therefore cannot anticipate an "effective amount" of HMGB1 or parts thereof. These arguments have been fully considered and are not found persuasive.

The instant specification provides examples of *in vitro* cell culture experiments wherein HMGB1 is administered in doses ranging from 1 – 100 ng/ml. Figure 3A of Tracey *et al* shows *in vitro* results of PBMCs cultured with HMGB1 ranging from 1 – 100 ng/ml. Thus, Tracey *et al* discloses an HMGB1 composition comprising HMGB1 at the same concentrations as taught by the instant application.

Furthermore, the degree of "treatment" of tissue damage, or of promotion of tissue repair or regeneration is not defined by the claims of the instant application. Thus, administration of any HMGB1 composition that mediates any effect on any tissue could be seen as "treating" tissue damage. The HMGB1 composition taught by Tracey *et al*, in the absence of evidence to the contrary, would undoubtedly mediate some degree of tissue repair or regeneration, and

would therefore constitute an "effective amount" of HMGB1 protein. Because the office does not have the facilities for testing and comparing the HMGB1 compositions of the instant application and that of Tracey *et al*, the burden is on the applicant to show a novel and unobvious difference between the claimed HMGB1 composition and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

Rejections maintained/necessitated by amendment

Claim 6 *remains rejected* under 35 USC § 103(a) as being obvious over Tracey *et al*. The subject matter of the instant application is discussed *supra*. Claim 6 is further drawn to the HMGB1 composition of claim 1 further comprising an anti-inflammation agent, and was rejected as being obvious over Tracey *et al* for reasons of record on page 9 of the previous office action mailed on 4/21/2006. In the response received on 8/21/2006, the Applicants argue that because Tracey *et al* does not teach treatment of tissue damage, tissue repair, or tissue regeneration, there is no motivation to use any effective amount for the claimed invention. Thus, Tracey *et al* cannot render obvious the effective amount of HMGB1 protein or parts thereof. These arguments have been fully considered and are not persuasive.

As set forth *supra* in the rejection under 35 U.S.C. 102(e), Tracey *et al* does in fact teach a composition comprising HMGB1 at the same concentrations as taught by the instant application. Furthermore, because the degree of treatment is not defined by the claims, the HMGB1 composition of Tracey *et al* would be expected to comprise an effective amount of HMGB1 to treat tissue damage, tissue repair, or regeneration. Thus, for the reasons set forth *supra*, Tracey *et al* does in fact teach an effective amount of HMGB1.

Conclusion

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

ROBERT S. LANDSMAN, PH.D
PRIMARY EXAMINER